INSULIN THERAPY IN DIABETES MELLITUS

"Insulin Is Not A Cure – It's Life Support."

INSIDE THE ISSUE:

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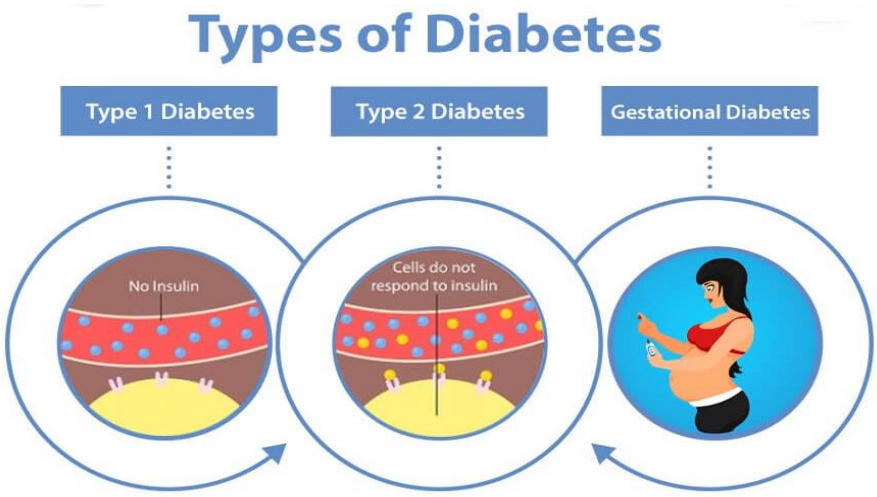
1. INTRODUCTION

Diabetes Mellitus is a disease that causes high blood sugar. The hormone insulin plays an important role to move sugar from the blood into body cells to be stored and used as energy. However, patient with diabetes may not have enough insulin in their body or their body did not effectively use the insulin that had been produced (insulin resistance) and leading to high blood glucose level. There are different types of diabetes including Type 1 diabetes, Type 2 diabetes and Gestational diabetes.

Figure 1: Types of Diabetes



Type 1 diabetes/insulin dependent diabetes:

An autoimmune disease that causes the insulin producing beta cells in the pancreas to be destroyed, preventing the body from being able to produce enough insulin to adequately regulate blood glucose levels. Type 1 diabetes may be referred as juvenile diabetes which is commonly diagnosed in children but also can develop at any age. Type 1 diabetes requires regular insulin administration to maintain the blood sugar level due to loss of insulin production. Lethal if leave untreated.

Type 2 diabetes/non-insulin dependent diabetes:

A metabolic disorder that results in high blood sugar level due to the body did not effectively using the insulin it had produced; which is also known as insulin resistance. Type 2 diabetes was formerly known as adult-onset diabetes due to its occurrence mainly in people over 40.

Gestational diabetes:

Gestational diabetes usually develops in the third trimester which is in between 24 and 28 weeks of pregnancy and typically disappears after the baby is born. Pregnant woman developed hormonal that resist insulin, along with the growth demands of the foetus, that increase a pregnant woman's insulin needs by two to three time that of normal.

GLYCAEMIC CONTROL FROM DIABETES MELLITUS:

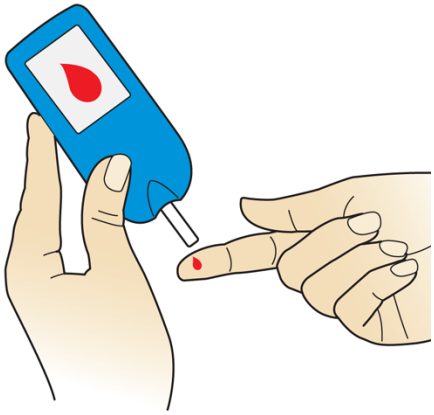
Table 1: Blood Glucose Targets in Different Glycemic Measures

Glycemic Measures	Targets
Fasting Blood Glucose (FBG)	4.4 – 6.1 mmol/L
Non- Fasting Blood Glucose	4.4 – 8.0 mmol/L
HbA1c	< 6.5%

Individualised targets for self-monitoring of blood glucose may be discussed after taking patient factors and limitations into consideration.

For people with type 2 diabetes mellitus (T2DM), the recommendations for how often to test blood sugar are based upon individual factors such as type of treatment (oral medications, insulin, and/or lifestyle changes). Self-monitoring blood glucose (SMBG) provides useful information and is an important part of managing the disease. It is helpful in patient with insulin as the blood sugar results will help to guide in choosing the appropriate doses from meal to meal. When patient first started on treatment, they will need to discuss with the health care provider to learn to make adjustments in treatment. However, with time and experience, most people are able to learn how to make adjustments on their own.

Figure 2: Self-Monitoring Blood Glucose



2. SIGN AND SYMPTOMS OF DIABETES

- Majority are asymptomatic.
- The first symptoms usually set in gradually, over a period of hours or days. They include polydipsia (increased thirst), polyuria (excessive urine production), lethargy, weight loss, blurring of vision and increased risk of infection.

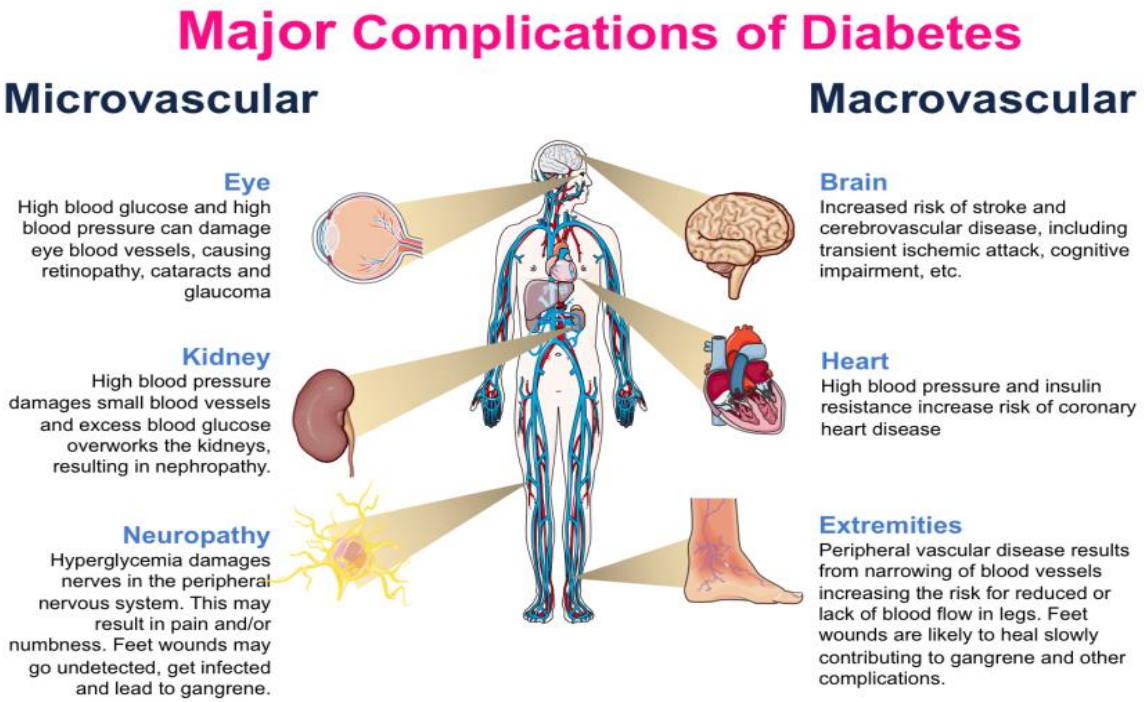
Figure 3: Symptoms of Diabetes Mellitus

3. COMPLICATIONS OF DIABETES

Diabetes complications are divided into two;

- Microvascular complications – due to the damage of small blood vessels.
- Macrovascular complications – due to the damage of larger blood vessel.

Figure 4: Major Complications of Diabetes Mellitus.



4. INITIATION OF INSULIN

Initiation of insulin means that starting of insulin. The initiation requires selection of appropriate insulin regimen, insulin type and starting dose to address the individual's main glycaemic control level.

The insulin regimen and insulin doses initiated are primarily individualised based on glucose profile as stated in table below.

Table 2: The Selection of Initial Insulin Regimen Based On Blood Sugar Profile.

Blood Glucose Profile		Preferred insulin regimen
Pre-Breakfast	Daytime	
High	Normal	Pre-bed intermediate / long acting insulin **(BASAL)**
High	High	Pre-bed intermediate / long-acting insulin and later add on prandial short / rapid acting insulin **(BASAL → BASAL PLUS / BASAL BOLUS) or (PRE-BREAKFAST AND PRE-DINNER PREMIXED INSULIN)**
Normal	High	Prandial short / rapid acting insulin and later add on basal insulin **(PRANDIAL → BASAL PLUS / BASAL BOLUS)**

Figure 5: The Selection of Insulin Regimen Based on individualized Blood Sugar Profile and Preferences

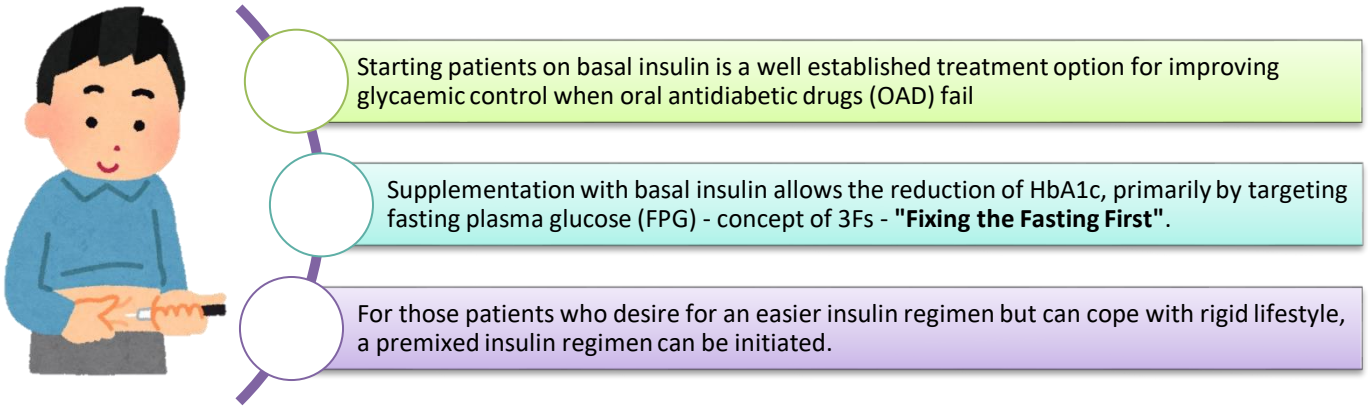


Table 3: Types of Insulin Regime, Initiation Dose, and Monitoring and Targets of Blood Glucose (BG).

Types of Regimen	Initiation Dose	Monitoring and Targets of Blood Glucose (BG)
Basal Insulin	10 units or 0.2U/kg at bedtime. (0.1 units/kg if higher risk for hypo)	Monitor pre-breakfast BG. Target pre-breakfast BG is at 4-6 mmol/L.
Premixed Insulin	Once daily: 10 units or 0.2U/kg at pre-dinner. Twice daily: 10 units or 0.2U/kg at pre-breakfast and pre-dinner. (0.1 units/kg if higher risk for hypo)	Once daily: Monitor pre-breakfast BG. Twice daily: Monitor pre-breakfast and pre-dinner BG. Target pre-meal BG is at 4-6 mmol/L.
Prandial Insulin	6 units or 0.1 units/kg for each meal with short-acting or rapid-acting analogue.	Pre-meals and pre-bed. (Postmeals 1.5-2 hours if using rapid-acting analogue) Target pre-meal BG: 4-6 mmol/L. Target post-meals and pre-bed: 4-8 mmol/L.
Basal-bolus Insulin	Prandial insulin: 6 units or 0.1U/kg before each meal. Basal insulin: 10 units or 0.2U/kg at bedtime.	Preferably 4 times per day upon initiation. Pre-meals at pre-breakfast, pre-lunch and pre-dinner and at bedtime. Target pre-meals BG: 4-6 mmol/L Target bedtime BG: 4-8 mmol/L

5. PHARMACOKINETIC PROFILES OF VARIOUS TYPES OF INSULIN

Pharmacokinetic data of insulin formulations with different onset and duration of action from several clinical studies were used to develop a predictive population pharmacokinetic model of insulin enabled informative visualization of insulin time-action profiles as below:

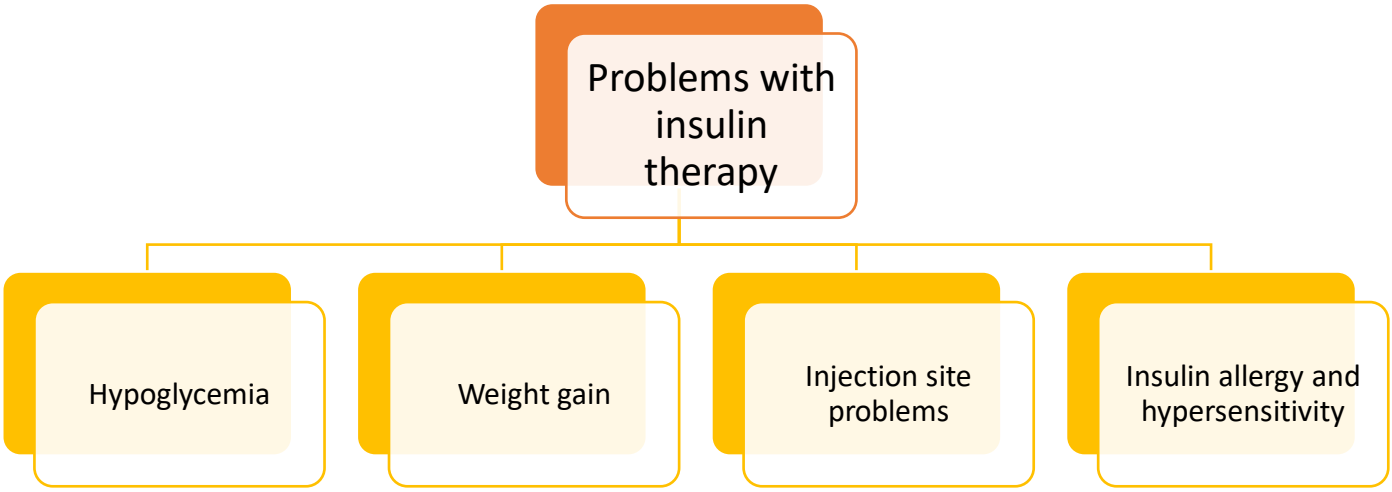
Table 4: Pharmacokinetic profiles of various types of insulin

Brand (Generic) Name	Onset	Peak (Hr)	Duration (Hr)	Timing of Insulin
- Actrapid - Insugen-R	30 min 30 min	1-3 2-4	8 6-8	30 mins before meal
b) Rapid-acting analogue - Novorapid (Aspart) - Humalog (Lispro)* - Apidra (Glulisine)*	 10-20 min 0-15 min 5-15 min	 1-3 1 1-2	 3-5 3.5-4.5 3-5	 5-15 mins before or immediately after meals
c) Intermediate-acting (Isophane/NPH) - Insulatard - Insugen-N	 1.5 Hr 1 Hr	 4-12 4-10	 18-23 16-28	 Pre-breakfast/ Pre-bed
d) Long-acting analogue - Lantus (Glargine) - Toujue (Glargine) - Levemir (Detemir)*	 2-4 Hr 6 Hr 1Hr	 Peakless Peakless Peakless	 20-24 > 24 17-23	 Same time everyday at anytime of the day
e) Premixed human (30% Regular insulin + 70% Isophane/NPH) - Mixtard 30 - Insugen 30/70	 30 min 30 min	 Dual Dual	 18-23 16-18	 30-60 mins before meals
f) Premixed analogue - NovoMix 30 (30% aspart + 70% aspart protamine) - Humalog Mix 25 (25% lispro + 75% lispro protamine)*	 10-20 min 0-15 min	 Dual Dual	 18-23 16-18	 5-15 mins before meals

** insulin unavailable in Hospital Queen Elizabeth II*

6. WAYS TO OVERCOME PROBLEMS ASSOCIATED WITH INSULIN THERAPY

Figure 6: Problems Associated with Insulin Therapy



A. Hypoglycaemia.

This problem has become progressively more frequent with advanced duration of type 2 diabetes mellitus (T2DM) and the use of intensive insulin therapy. Hypoglycaemia has a negative impact on physical and psychological well-being. Hypoglycaemia and fear of hypoglycaemia are important limiting factors in glycaemic management and may become significant barriers to treatment adherence as patients may stop taking their medications which may results in poor glycaemic control. Severe hypoglycaemias can increase the fear of future hypoglycaemic events. Hence, patients with T2DM may maintain their blood glucose levels with a 'safety margin', for instance at higher than recommended values and maintain hyperglycaemia in order to reduce hypoglycaemic events. Fear of hypoglycaemia can be avoided through awareness of the causes of low blood glucose and good communication between patient and clinician to ensure optimal use insulin therapy in patients with T2DM.

Figure 7: Symptoms of Hypoglycaemia

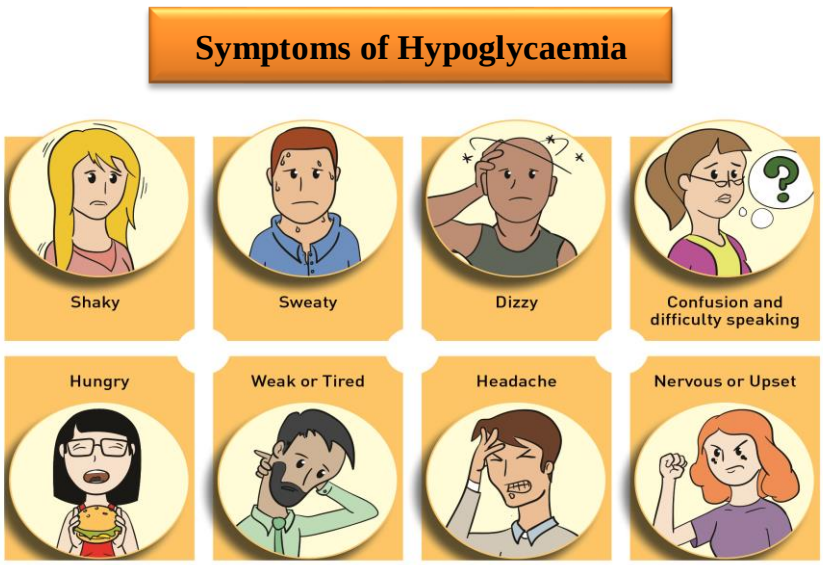


Figure 8: Treatment of Hypoglycaemia

Treatment of Hypoglycaemia

1. Assess the cause and severity of hypoglycaemia.
2. Treat hypoglycaemia according to BG level.
   - **Mild** (BG 3.3-3.9 mmol/L): Give 15g carbohydrate
     - 4 ounces (120ml) orange juice or other fruit juices **OR**
     - Hard candy **OR**
     - 3 glucose tablets
   - **Moderate** (BG 2.5-3.2 mmol/L): Give 20g carbohydrate
     - 6 ounces (180ml) orange juice or other fruit juices **OR**
     - 4 glucose tablets **OR**
     - Dextrose 50% 25ml IV
   - **Severe** (BG < 2.5 mmol/L): Give 30g carbohydrate
     - 8 ounces (240ml) orange juice or other fruit juices **OR**
     - 6 glucose tablets **OR**
     - Dextrose 50% 25ml IV
   - **Unconscious with severe hypoglycaemia** (BG < 2.5 mmol/L)
     - Dextrose 50% 25ml IV **OR**
     - Glucagon 1mg subcutaneous or intramuscular (0.5mg for child)
       - Vomiting and aspiration risk
       - Roll patient onto their side when used
3. Monitor BG level every 15 minutes until > 5.6 mmol/L.
4. Redose glucose replacement as above every 15 minutes as necessary (PRN).

B. Weight gain

Insulin therapy commonly results in weight gain and it can be excessive, adversely affecting cardiovascular risk profile. The spectre of weight gain can increase diabetic morbidity and mortality when it acts as a psychological barrier to the initiation or intensification of insulin, or affects adherence with prescribed regimens.

Table 5: Factors and Steps to Counter Weight Gain

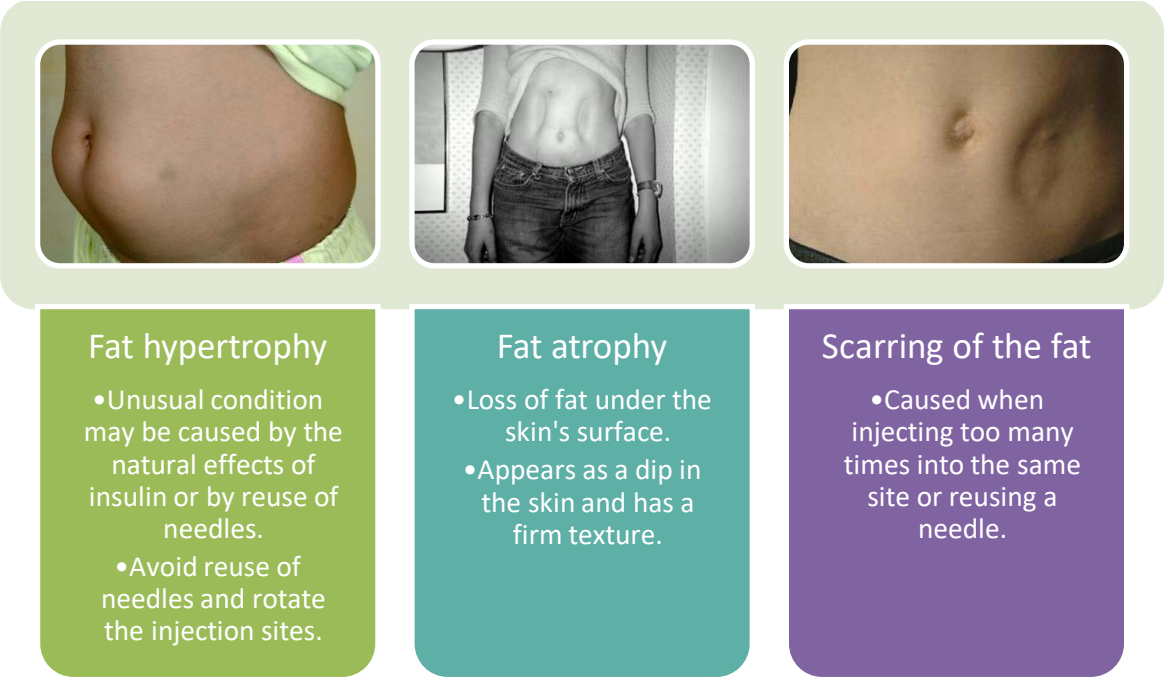
Factors	Steps to Counter Weight Gain
1. Increases metabolic control. 2. Fear of hypoglycaemia → lead to increased snacking between meals. 3. Use of insulin can increase lean body mass through its anabolic nature. 4. Insulin use can also cause salt and water retention.	1. Restrict calories and portion control. 2. Appropriate advice from dietician. 3. Keep physically active and practise regular exercise. 4. Avoid high doses of insulin → reducing carbohydrate intake and being physically active reduces insulin requirement.

The healthcare team can help to plan to counter weight gain in insulin therapy by assessing the patient's conditions such as by body mass index (BMI), overall health status and obstacles which patients may encounter in terms of diet and physical activity. Exercise is one of the best ways to prevent insulin-associated

weight gain. The American Heart Association recommends of at least 150 minutes of moderate exercise each week for adults which is equivalent to 30 minutes of exercise five days a week. Patients with type 2 diabetes mellitus can improve their insulin sensitivity with moderate-intensity resistance training.

C. Injection site problems

Figure 9: Injection Site Problem



Precautions for insulin injections must be practiced to prevent the associated skin lesions. Tips for preventing injection site problems:

- Rotate the injection site for each time of injection.
- Keep track of the injection locations (can use chart or even an app to keep track).
- Ensure to use a fresh needle each time of injection (it is advisable to use the needle to maximum of three times use only).
- When injecting near a previous injection site, leave about an inch of space in between the two.

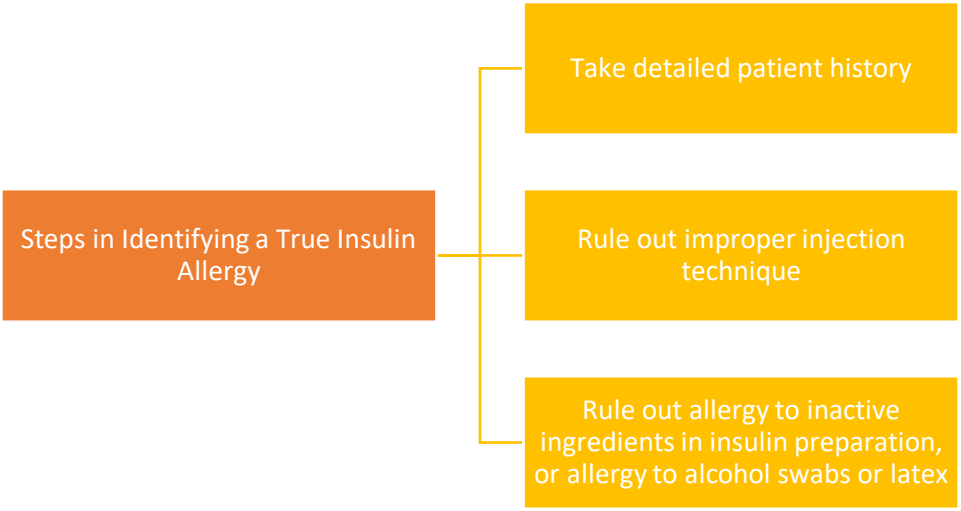
Insulin absorbs at different rates depending on the site of injection. In general, the abdomen absorbs injected insulin the fastest. The arm would be second and the third fastest is in the thigh area. It is important to routinely inspect the injection sites for signs of fat hypertrophy, fat atrophy and scarring of the fat. Initially, the bumps are not seen however, firmness can be felt under the skin. The area will then will be less sensitive and less feeling of pain when injecting insulin.

D. Insulin allergy and hypersensitivity

Insulin allergies are rare and most allergic reactions are restricted to the skin and are either local immediate or delayed reaction type. Immediate reactions generally develop within one hour after an injection and often much more quickly. These rare reactions range from local erythema or a pruritic wheal at the injection site to systemic anaphylaxis that may involve generalised urticaria, pruritus, angioedema or

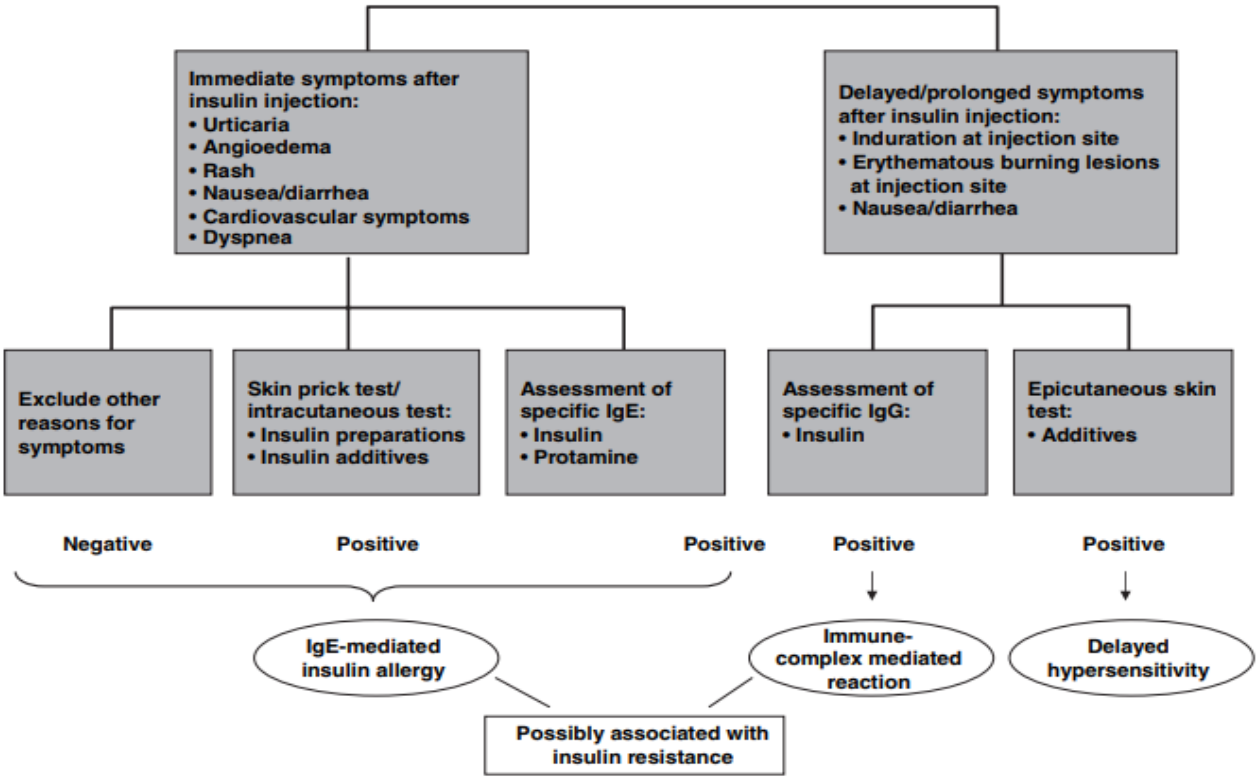
hypotension. Delayed reactions develop later than one hour and typically between 6 and 24 hours. Common presentations include eczematous skin changes or induration or nodules at the site of injection. Delayed reactions usually resolve spontaneously with time. If insulin allergy is suspected in a patient, it is important to take proper steps in identifying a true insulin allergy.

Figure 10: Steps in Identifying a True Insulin Allergy



Improper injection technique can mimic an allergic reaction, hence it must be ruled out first. If proper injection technique is confirmed, the next step is to switch to another type insulin as it is common to be allergic to inactive ingredients in the insulin preparation such as protamine sulfate, zinc, metacresol, sodium phosphate, phenol and glycerol. If switching to a different type of insulin does not resolve the problem, it is likely patient is allergic to the insulin molecule itself and should be immediately referred for further testing.

Figure 11: Diagnostic approach in suspected insulin allergy



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